PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Metallic Compounds of Amino Acids and Preparation thereof

We, MEDICAL RESEARCH PROPRIETARY LIMITED, a company incorporated in the State of New South Wales, Commonwealth of Australia, of Scot Chambers, Hosking Place, Sydney, New South Wales, Australia, do hereby declare the nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

In the past many different organic compounds of iron have been incorporated in foods and have otherwise been prepared for medical purposes. Examples of such compounds are those of iron and ammonium citrate, thio-compounds in conjunction with organic acid radicals, ferrous and ferric gluconates and the like. As such compounds are not in a highly biochemically active form, it has been necessary to administer them in very large doses, in some cases up to 90 grains per day. By this invention organic compounds of iron, are prepared in a highly active form, that is, in a form which very closely approximates to the form in which iron is contained in blood hæmoglobin or other body fluids. It follows that advantages due to the present invention are that dosages may be considerably reduced, by comparison with what has been regarded as normal dosage heretofore, due to the compounds subject hereof being much more readily and much more completely capable of assimilation.

To be of any appreciable metabolic value iron must be in combination with amino acids, and it is believed that in so far as iron has been capable of assimilation by humans or animals it is because it is converted to this amino acid form within the alimentary system. So far as is known, iron compounds of all the amino acids derivable from a proteinous material have not hitherto been synthesised as a readily assimilable group other than within a living human or animal body as a metabolic function thereof. The present invention has been devised to synthesize iron compounds with all the amino acids obtainable from a common proteinous material thus to provide an admixture of amino acid salts which closely approaches the complex amino acid salt admixture present in natural hæmoglobin.

The method subject hereof consists in the preparation of a complex admixture of amino acid salts of iron in a form substantially the same as that of the amino acid salts of iron occurring in natural hæmoglobin, comprising the steps of enzymatically digesting a proteinous material to free amino acids therefrom; and, without separating any of said acids, reacting the entire admixture thereof with an iron compound selected from the group consisting of the hydroxides, hydrated oxides and carbonates of iron. The reaction of the amino acid admixture with the iron compound may be carried out at ordinary room temperatures, but for preference (in order to shorten the reaction time) the reaction is carried out at an elevated temperature, of the order, for example, of 60–80° C. If desired, the step of reacting the amino acids with the iron compound may consist in first reacting the amino acid admixture with a soluble salt of sodium or other metal other than iron, and then forming the required complex admixture of amino acid salts by double decomposition between the amino acid salts of the metal other than iron with an iron salt.

Practically any protein substance may be employed as starting material herein. Such substance may be casein, gelatine, yeast, soya bean flour, egg albumen, vegetable or animal albumen or a mixture of two or more such protein substances in any proportions.

The ph value of the protein is first adjusted in accordance with the nature of the protein used and the enzymes to be used in the digestion.

The digestion may be carried out under acid, neutral or alkaline conditions. With acid digestion pepsin is added to the proteins as an enzymatic or catalytic agent. The

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amount of pepsin may vary from the merest trace up to as much as or more than 10 per cent by weight of the proteins. In the case of neutral digestion the preferred enzymatic or catalytic agent is papain used in the same quantities as indicated above, with alkaline digestion the preferred enzymatic agent is pancreatic extract also in the same proportions. After addition of the enzymatic agent the temperature of the batch is adjusted to give optimum enzymatic action. This temperature may be from about 35° to 40° C. Digestion is then allowed to proceed, giving an admixture of amino acids, polypeptones and the like, and unconverted proteins. It will be understood that depending on the progress of the digestion and the nature of the proteinous matters used, the digestion may be carried out in several stages, in some of which the ph value may be varied so that a digestion which commenced as an acid process is carried on as a neutral or alkaline process, the procedure being varied to give a high amino acid yield; and, as far as possible, to exhaust the proteins present. The mixture resulting from digestion then has its ph value adjusted to from 3·6 to 4·6 (preferably about 4), that is, if it is not already of about this hydrogen ion concentration. This frees the amino acids from combination. For many medicinal uses it is not harmful for the salts, peptides, unconverted proteins and other matters to remain with the amino acids.

To produce an iron compound or compounds with the amino acids, a soluble salt or salts of iron is or are converted to hydrate, hydroxide or carbonate form. The hydroxide form is preferable and may be brought about by addition of caustic soda or other alkali. In either case this action gives a precipitation which, if required, enables unwanted salts or the like to be removed. Alternatively, such salts may be allowed to remain if they are biochemically unobjectionable or in some cases medicinally desirable (as may be the case where glauber salts or other medicinal agents are formed). The iron hydrate, hydroxide or carbonate is then mixed with the amino acids still in accompaniment with unconverted proteins, peptones and the like in such proportions as will give the resultant mixture a ph value equal or about equal to from 6·5 to 7. This admixture is sufficient to give the required iron compounds of the amino acids. A typical example of the invention is set forth below.

EXAMPLE

MANUFACTURE OF A COMPLEX BIOLOGICALLY ACTIVE IRON COMPOUND

5 pounds of casein, 2 pounds of gelatine, and 70 pounds of water are mixed and the resulting solution subjected to enzymatic hydrolysis by the addition of approximately 20 grammes of pancreatic extract.

Sufficient sodium carbonate is added to adjust the ph to between 7·3 and 8·0 and the whole maintained at a temperature of between 38/40° centigrade until hydrolysis has reached a stage where between 60 and 70% at least of the protein is hydrolized.

The above solution is then adjusted to a ph 4·3 by the addition of sulphuric acid, when a previously prepared hydroxide of iron is added to the amino acid hydrolysate and the whole thoroughly agitated and maintained at a temperature of between 60 and 80° centigrade (preferably under vacuum) until ph of 6·5 to 7·0 is obtained.

The clear solution obtained after filtration is concentrated to any degree or to dry powder form as required.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A method of preparing a complex admixture of amino salts or iron in a form substantially the same as that of the amino acid salts of iron occurring in natural hæmoglobin, comprising the steps of enzymatically digesting a proteinous material to free amino acids therefrom, and, without separating any of said acids, reacting the entire admixture thereof with an iron compound selected from the group consisting of the hydroxides, hydrated oxides and carbonates of iron.

2. A method according to Claim 1, wherein the said step of reacting an entire admixture of amino acids with an iron compound is carried out at an elevated temperature.

3. A method according to Claim 1, wherein the said step of reacting an entire admixture of amino acids with an iron compound, consists in first reacting the amino acids of said admixture with a soluble salt of a metal other than iron, and then forming the required complex admixture of amino acid salts by double decomposition between said amino acid salts of a metal other than iron with an iron salt.

4. A method according to Claim 1, wherein the step of digesting a proteinous material is performed under alkaline conditions and by use of pancreatic extract as enzymatic agent.

5. A complex admixture of amino acid salts of iron when prepared by a method according to any of the preceding claims.

Dated this 16th day of June, 1948.

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